IMAGING EARLY MARKERS OF DIABETIC MICROVASCULAR COMPLICATIONS IN PERIPHERAL TISSUE

Release Date: November 26, 2001

RFA: RFA-DK-02-001

National Institute of Diabetes and Digestive and Kidney Diseases
(http://www.niddk.nih.gov)
National Institute of Arthritis and Musculoskeletal and Skin Diseases
(http://www.niams.nih.gov)

Letter of Intent Receipt Date: February 15, 2002
Application Receipt Date: March 15, 2002

THIS RFA USES "MODULAR GRANT" AND "JUST-IN-TIME" CONCEPTS. MODULAR INSTRUCTIONS MUST BE USED FOR RESEARCH GRANT APPLICATIONS REQUESTING LESS THAN $250,000 PER YEAR IN ALL YEARS. MODULAR BUDGET INSTRUCTIONS ARE PROVIDED IN SECTION C OF THE PHS 398 (REVISION 5/2001) AVAILABLE AT http://grants.nih.gov/grants/funding/phs398/phs398.html.

PURPOSE

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) solicit applications for studies designed to apply imaging techniques that measure perfusion or tissue oxygenation at the level of the microvasculature to the study of diabetes and its complications. Although the etiology of peripheral microvasculature complications in diabetic patients is not known, defective perfusion may be an early event. If so, very early detection of changes in perfusion or oxygenation may help to identify those patients that are at risk for the microvascular complications of diabetes such as neuropathy that can lead to loss of sensation and the development of foot ulcers. Once identified, these patients can be specially flagged for intensive treatment in hopes of preventing complications. The ability to image inflammation and angiogenesis in peripheral tissues may help to assess wounds and develop optimal treatment plans as well as to monitor wound healing in diabetes, and to identify those patients who have sufficiently impaired perfusion that they would benefit from revascularization procedures. The ultimate goal of this initiative is to provide the diabetes clinical community with reliable, inexpensive tools to study the mechanisms leading to

the microvascular complications of diabetes in peripheral tissues, to detect the early stages of these complications, identify patients likely to benefit from therapeutic interventions, and monitor disease progression and response to therapy.

A separate RFA, "Surrogate Markers for Diabetic Microvascular Complications", DK-02-016 from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Eye Institute (NEI) and the National Institute of Neurological Disorders and Stroke (NINDS), http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-02-016.html invites basic and clinical research applications to develop a large range of biochemical, cellular, physiologic and genetic surrogate markers that can be used to predict risk, aid in early diagnosis and assess progression of all microvascular complications of diabetes.

HEALTHY PEOPLE 2010

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This Request for Applications (RFA), "Imaging Early Markers of Diabetic Microvascular Complications in Peripheral Tissue," is related to the priority area of diabetes and chronic disabling conditions. Potential applicants may obtain a copy of "Healthy People 2010" at http://www.health.gov/healthypeople/.

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic and foreign for-profit and nonprofit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as principal investigators.

MECHANISM OF SUPPORT

This RFA will use the National Institutes of Health (NIH) research project grant (R01) and Pilot and Feasibility (R21) award mechanisms. Responsibility for the planning, direction, and execution of the proposed project will be solely that of the applicant. The total project period for an application submitted in response to this RFA may not exceed 4 years for the R01 and 2 years for the R21 mechanism.

Specific application instructions have been modified to reflect "MODULAR GRANT" and "JUST-IN-TIME" streamlining efforts that have been adopted by the NIH. Complete and detailed instructions and information on Modular Grant applications have been incorporated into the PHS 398 (rev. 5/2001). Additional information on Modular Grants can be found at http://grants.nih.gov/grants/funding/modular/modular.htm

This RFA is a one-time solicitation. Future unsolicited competing continuation applications will compete with all investigator-initiated applications and be reviewed according to the customary peer review procedures. The anticipated award date is September 30, 2002.

FUNDS AVAILABLE

The NIDDK and NIAMS intend to commit approximately $1.0 million in FY 2002 to fund 3 to 5 new grants in response to this RFA. Because the nature and scope of the research proposed may vary, it is anticipated that the size of each award will also vary. An applicant may request a project period of up to 4 years using the R01 mechanism. All applications requesting $250,000 direct costs per year or less must use the modular budget format. R21 Pilot and Feasibility grant applications should request 2 years at up to $100,000 direct costs per year. These applications should propose innovative high risk, high yield research, and do not require the extensive preliminary data necessary for an R01 application. Although the financial plans of the NIDDK and NIAMS provide support for this program, awards pursuant to this RFA are contingent upon the availability of funds and the receipt of a sufficient number of applications of outstanding scientific and technical merit. At this time, it is not known if this RFA will be reissued.

RESEARCH OBJECTIVES

Background

The Diabetes Control and Complications Trial (DCCT) for type 1 diabetes, and the United Kingdom Prospective Diabetes Study (UKPDS) for type 2 diabetes demonstrated that intensive control of blood glucose levels could dramatically reduce the devastating microvascular complications of diabetes. The UKPDS also demonstrated a benefit of rigorous blood pressure control in preventing microvascular complications. In the DCCT development of complications was reduced both in patients without discernable microvascular damage and in those with evidence of early retinopathy at the start of the study. Thus patients identified at an early stage in the development of microvascular disease would have a special incentive to maintain good control of their blood glucose in an attempt to avoid future health problems.

Although much work remains to be done to determine the specific events that lead to the microvascular complications of diabetes, damage to the endothelial cell layer in the vessels themselves by alterations in cytokines, nitric oxide, superoxides, advanced glycation endproducts, increased vascular endothelial growth factor, etc. may lead to alterations in vessel elasticity, leakiness, tissue perfusion and oxygenation. It may be possible to use modern imaging technologies, coupled with exercise or a vasoactive compound such as nitric oxide, to identify and localize parameters that correlate with an increased risk for developing microvascular diabetic complications. Candidate parameters might be blood flow or volume, water diffusion, myoglobin or hemoglobin oxygenation, cytochrome oxidation state, or altered kinetics of contrast agent extravascularization. Patients with established microvascular disease are at increased risk of foot ulceration that may progress and lead to amputation. It is often difficult to assess the extent of a lesion, and patients with what appear to be superficial ulcers may benefit from the ability to locate and visualize the extent of inflammation to determine the optimal therapeutic approach. The ability to monitor blood flow or angiogenesis may also allow doctors to document early responses to therapy for wound healing. Angiography with contrast agents is associated with risks, particularly for patients with diabetic nephropathy. A non-invasive method of assessing circulation in the limbs of diabetic patients is needed that could identify patients who are good candidates for revascularization surgery. Any of these phenomena may also serve as surrogate markers in future clinical trials of prevention or treatment of microvascular complications, or may aid basic research to understand the pathogenesis of neuropathy. The ideal technologies would be fairly easy to implement, require relatively little training of clinic personnel, and be inexpensive or employ already widely distributed medical equipment.

A variety of new spectroscopic and imaging technologies could provide direct and indirect measures of blood flow and tissue oxygenation with fine spatial resolution. MRI, optical imaging, and ultrasound can be used to measure blood flow and blood volume. In the brain, blood oxyhemoglobin serves as an MRI contrast agent that is sensitive to neural activation. Other measurements of tissue oxygenation have been provided by optical spectroscopy of the oxidation states of cytochromes, hemoglobin and myoglobin. New methodologies such as optical tomography make the optical imaging of deep tissues possible. MRI is also used to measure the diffusion of water through tissue. In normal muscle and neural tissue, diffusion is constrained by the muscle fibers and nerve sheath. Disruptions in these structures due to ischemia and hypoxia, or due to other types of damage secondary to diabetes may be detectable using MRI. The behavior of injected contrast agents may allow the detection of pathological microvessel characteristics such as leakiness, loss of patency, or obstruction.

A distinct but similar methodology, molecular imaging, uses contrast agents bound to antibodies or other targeting molecules that 'light up' specific cell types or sub-organ structures. By exploiting the unique surface molecules expressed in growing vascular tissue and in cells of the immune system, molecular imaging has been successfully used to visualize angiogenesis and inflammation. This might be valuable for monitoring wound healing, adequacy of debridment, and the extent of tissue involvement in patients with diabetic foot disease, a particular interest of NIAMS.

Scope and Objectives

This RFA is intended to support research using animals or human subjects, development of equipment to help manage diabetes in the clinic, and limited clinical trials to test the utility of potential methodologies for monitoring microvascular disease in the diabetic population. Collaborations between scientists with expertise in imaging and those with expertise in diabetic complications, or with animal models of diabetes, are encouraged. Appropriate topics for investigation under this RFA would include but are not limited to:

o Investigation of the relationship between blood flow, tissue perfusion, diffusion, oxygenation, non-toxic contrast agent kinetics, etc. in peripheral tissues and the development of diabetic microvascular complications;

o Evaluation of imageable parameters in peripheral tissues as markers for very early microvascular disease in diabetes;

o Evaluation of imageable parameters as markers of nerve damage in peripheral tissues;

o Application of imaging technology to identify areas of infection, or evaluate the extent of infection, in patients with foot ulceration due to diabetes. Emphasis would be on those technologies that could easily be translated to the clinic;

o Application of imaging technology to monitor the growth of new blood vessels during therapy for injuries such as foot ulcers related to diabetic complications, or identify those patients that would benefit from procedures to restore circulation;

o Application of imaging technology to enhance understanding of the etiology and mechanism of peripheral diabetic microvascular complications;

o Development of new machines (inexpensive, robust, portable) for imaging blood flow, oxygenation, etc. for the management of diabetes and its complications in the clinic or hospital environment;

o Small clinical trials designed to apply imaging technology to measure perfusion, diffusion, oxygenation, angiogenesis, or inflammation and their role in complications in the diabetic population.

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH-supported clinical research projects unless a clear and compelling justification is provided indicating that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing clinical research should read the AMENDMENT "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research - Amended, October, 2001," published in the NIH Guide for Grants and Contracts on October 9, 2001 (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html);
a complete copy of the updated Guidelines are available at http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm.
The amended policy incorporates: the use of an NIH definition of clinical research; updated racial and ethnic categories in compliance with the new OMB standards; clarification of language governing NIH-defined Phase III clinical trials consistent with the new PHS Form 398; and updated roles and responsibilities of NIH staff and the extramural community. The policy continues to require for all NIH-defined Phase III clinical trials that: a) all applications or proposals and/or protocols must provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) investigators must report annual accrual and progress in conducting analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of NIH that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them.
This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects" that was published in the NIH Guide for Grants and Contracts, March 6, 1998, and is available at the following URL address: http://grants.nih.gov/grants/guide/notice-files/not98-024.html.

Investigators may also obtain copies of these policies from the program staff listed under INQUIRIES. Program staff may also provide additional relevant information concerning the policy.

REQUIRED EDUCATION ON THE PROTECTION OF HUMAN SUBJECT PARTICIPANTS

NIH policy requires education on the protection of human subject participants for all investigators submitting NIH proposals for research involving human subjects. This policy announcement is found in the NIH Guide for Grants and Contracts Announcement dated June 5, 2000, at the following website: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html.

URLS IN NIH GRANT APPLICATIONS OR APPENDICES

All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Reviewers are cautioned that their anonymity may be compromised when they directly access an Internet site.

PUBLIC ACCESS TO RESEARCH DATA THROUGH THE FREEDOM OF INFORMATION ACT

The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is

important for applicants to understand the basic scope of this amendment. NIH has provided guidance at:http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm

Applicants may wish to place data collected under this RFA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

LETTER OF INTENT

Prospective applicants are asked to submit, by February 15, 2002, a letter of intent that includes a descriptive title of the proposed research; the name, address, and telephone number of the Principal Investigator; the identities of other key personnel and participating institutions; and the number and title of the RFA in response to which the application may be submitted.

Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows NIDDK staff to estimate the potential review workload and plan the review.

The letter of intent is to be sent to:

Chief, Review Branch
Division of Extramural Activities, NIDDK
6707 Democracy Boulevard, Rm. 752 MSC 5452
Bethesda, MD 20892-5452
(for express/courier service: Bethesda, MD 20817)
Telephone: (301) 594-8897
FAX: (301) 480-3505

APPLICATION PROCEDURES

The PHS 398 research grant application instructions and forms (rev. 5/2001) at http://grants.nih.gov/grants/funding/phs398/phs398.html must be used in applying for these grants. This version of the PHS 398 is available in an interactive, searchable format. The NIH will

return applications that are not submitted on the 5/2001 version. For further assistance contact GrantsInfo, Telephone 301/435-0714, Email: GrantsInfo@nih.gov.

All application instructions outlined in the PHS 398 application kit are to be followed, with the following requirements for R21 applications:

1. R21 applications will use the "MODULAR GRANT" and "JUST-IN-TIME" concepts, with direct costs requested in $25,000 modules, up to the total direct costs limit of $100,000 per year.

2. Although preliminary data are not required for an R21 application, they may be included.

3. Sections a-d of the Research Plan of the R21 application may not exceed 15 pages, including tables and figures.

4. R21 appendix materials should be limited, as is consistent with the exploratory nature of the R21 mechanism, and should not be used to circumvent the page limit for the research plan. Copies of appendix material will only be provided to the primary reviewers of the application and will not be reproduced for wider distribution. The following materials may be included in the appendix:

o Up to five publications, including manuscripts (submitted or accepted for publication), abstracts, patents, or other printed materials directly relevant to the project. These may be stapled as sets.
o Surveys, questionnaires, data collection instruments, and clinical protocols. These may be stapled as sets.
o Original glossy photographs or color images of gels, micrographs, etc., provided that a photocopy (may be reduced in size) is also included within the 15 page limit of items a-d of the research plan

SPECIFIC INSTRUCTIONS FOR MODULAR GRANT APPLICATIONS

The modular grant concept establishes specific modules in which direct costs may be requested as well as a maximum level for requested budgets. Only limited budgetary information is required under this approach. The just-in-time concept allows applicants to submit certain information only when there is a possibility for an award. It is anticipated that these changes will reduce the administrative burden for the applicants, reviewers and NIH staff. The research grant application form PHS 398 (rev. 5/2001) at http://grants.nih.gov/grants/funding/phs398/phs398.html is to be

used in applying for these grants, with modular budget instructions provided in Section C of the application instructions.

The RFA label available in the PHS 398 (rev. 5/2001) application form must be affixed to the bottom of the face page of the application. Type the RFA number on the label. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the RFA title and number must be typed on line 2 of the face page of the application form and the YES box must be marked. The RFA label is also available at: http://grants.nih.gov/grants/funding/phs398/label-bk.pdf.

Submit a signed, typewritten original of the application, including the Checklist, and five signed photocopies, in one package to:

Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040 - MSC 7710
Bethesda, MD 20892-7710
Bethesda, MD 20817 (for express/courier service)

Applications must be received by the application receipt date listed in the heading of the RFA. If an application is received after that date, it will be returned to the applicant without review. Supplemental documents containing significant revision or additions will not be accepted, unless applicants are notified by the Scientific Review Administrator.

The Center for Scientific Review (CSR) will not accept any application in response to this RFA that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. The CSR will not accept any application that is essentially the same as one already reviewed. This does not preclude the submission of substantial revisions of applications previously reviewed, but such applications must include an Introduction addressing the previous critique.

REVIEW CONSIDERATIONS

Upon receipt, applications will be reviewed for completeness by the CSR and responsiveness by the NIDDK and NIAMS. If the application is not responsive to the RFA, NIDDK, NIAMS or CSR staff may contact the applicant to determine whether to return the application to the applicant or submit it for review in the competition with unsolicited applications at the next review cycle.

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by the NIDDK in accordance with the review criteria stated below. As part of the initial merit review, all applications will receive a written critique and undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of the applications under review, will be discussed, assigned a priority score, and receive a second level review by the NIDDK and NIAMS Advisory Councils.

Review Criteria

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written comments, reviewers will be asked to discuss the following aspects of the application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered in assigning the overall score, weighting them as appropriate for each application. Note that the application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

(1) Significance: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

(2) Approach: Are the conceptual framework, design, methods, and analyses adequately developed, well integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

(3) Innovation: Does the project employ novel concepts, approaches or methods? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

(4) Investigator: Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

(5) Environment: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

In addition to the above criteria, in accordance with NIH policy, all applications will also be reviewed with respect to the following:

o Adequacy of plans to include both genders, minorities and their subgroups, and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated.

o The reasonableness of the proposed budget and duration to the proposed research.

o The adequacy of the proposed protection of humans, animals, or the environment, to the extent that they may be adversely affected by the project proposed in the application.

o Availability of special opportunities for furthering research programs through the use of unusual talent resources, populations, or environmental conditions in other countries which are not readily available in the United States or which provide augmentation of existing U.S. resources.

Schedule

Letter of Intent Receipt Date: February 15, 2002
Application Receipt Date: March 15, 2002
Peer Review Date: July 2002
Council Review: September 2002
Earliest Anticipated Start Date: September 30, 2002

AWARD CRITERIA

Award criteria that will be used to make award decisions include:

o Scientific merit as determined by peer review;
o Availability of funds;
o Programmatic priorities.

INQUIRIES

Inquiries concerning this RFA are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Direct inquiries regarding programmatic issues to:

Maren R. Laughlin, Ph.D.
Division of Diabetes, Endocrinology and Metabolic Diseases
National Institute of Diabetes and Digestive and Kidney Diseases
6707 Democracy Boulevard, Rm. 6101 MSC 5460
Bethesda, MD 20892-5460
Telephone: (301) 594-8802
FAX: (301) 480-3503
E-mail: ml33q@nih.gov

Alan N. Moshell, M.D.
Director, Skin Diseases Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Building 45, Room 5 AS-25L
45 Center Drive MSC 6500
Bethesda, MD 20892-6500
Telephone: (301) 594-5017
FAX: (301) 480-4543
Email: am40j@nih.gov

Direct inquiries regarding fiscal matters to:

Denise Payne
Division of Extramural Activities
National Institute of Diabetes and Digestive and Kidney Diseases
6707 Democracy Boulevard, Rm. 733 MSC 5456
Bethesda, MD 20892-5456
Telephone: (301) 594-8845
FAX: (301) 480-3504
E-mail: dp43b@nih.gov

AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.847 and No. 93.846. Awards are under authorization of the Public Health Service Act, Title IV, Part A (Public Law 78-410, as amended by Public Law 99-158, 42 USC 241 and 285) and administered under NIH grants policies and Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The PHS strongly encourages all grant and contract recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

Return to Volume Index
Return to NIH Guide Main Index